Page 14, line 15, change "LPV" to --KPV--.

Page 15, lines 6 and 23, change "LPV" to --KPV--.

Page 16, line 3, change "LPV" to --KPV--.

REMARKS

Entry of the foregoing amendments, reconsideration and reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, and in light of the remarks which follow, are respectfully requested.

By the present amendments, the composition claims have been cancelled in favor of method claims. Therefore, as a result of the present amendments, all of the claims are now directed to usage of lysine-proline-valine containing peptides for treatment of inflammation. Also, the claims and specification have been amended in order to obviate informalities. These amendments are made in order to expedite prosecution.

Turning now to the Office Action, the Examiner's consideration of the Information Disclosure Statement is noted.

The disclosure stands objected to as assertedly containing informalities. In particular, the Examiner indicates that an incorrect designation for the lysine amino acid residue has been used. While it is believed that the claims would be clear in

light of the specification, in order to avoid any potential confusion, Applicants have changed LPV at all occurrences to KPV. Also, the Examiner asks what is the difference between the peptides recited in Table IV. Applicants respectfully note that these peptides differ by whether the dextrorotatory or levorotatory isomeric forms of lysine, proline, or valine are contained therein. The exact structure of these peptides would be apparent based on the disclosure at page 16, lines 6-8, wherein such peptides are defined by Applicants. Therefore, withdrawal of the objections to the specification are respectfully requested.

Also, Claim 4 stands objected as being an improper multiple dependent claim. This objection should be moot, as Claim 1 has been amended to recite that lysine or valine can exist in either their dextrorotatory or levorotatory isomeric forms.

Claims 1-15 stand rejected under 35 U.S.C. §112, first paragraph, as being broader than the enabling disclosure. This rejection is respectfully traversed. Applicants respectfully submit that practice of the claimed invention would not rise to the level of the undue experimentation. As discussed in the subject application, Applicants have surprisingly discovered that peptides comprising the lysine-proline-valine tripeptide sequence, wherein the proline moiety exists in its dextrorotatory isomeric form, exhibit anti-inflammatory activity. This activity is substantiated by the results contained in the examples at pages 9-16 of the subject application.

Therefore, based on this discovery, one skilled in the art could, absent the exercise of undue experimentation, produce fusion polypeptides containing this sequence and screen for those exhibiting anti-inflammatory activity. Contrary to the Office Action, this would not rise to the level of undue experimentation, as the subject application provides assays for identifying operative embodiments. In particular, such anti-inflammatory activity can be evaluated by assaying inflammatory activity according to the dose-response assay which measures the ability of this peptide to inhibit the production of interleukin 1 alpha in a supernatant containing plucked hairs. This is a suitable assay, as such cytokines are characteristically produced during inflammatory responses. Therefore, the ability to inhibit the expression of such cytokines is an effective means of determining whether a particular peptide inhibits inflammation. Therefore, based on the foregoing, withdrawal of the §112, first paragraph, rejection of Claims 1-15 is respectfully requested.

Claims 1-15 further stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is respectfully traversed to the extent it may be applicable to the claims as amended.

Claims 1 and 3 are indicated to be indefinite in the recitation "existing" rather that --exist--. This objection should be moot as existing has been changed to exist, as suggested by

the Examiner. Also, the objection with respect to "functional biological equivalent thereof" is moot as this phrase has been cancelled from Claim 1. Also, the Examiner's query with respect to "at the C-terminal end" should be moot, as the claims have been amended to recite that the tripeptide constitutes the last three amino acids at the C terminus of the peptide. Also, the objection to Claim 5 is believed to have been obviated because the claim now recites that the protecting group may be located either at the C-end or N-end of the peptide. This is consistent with the disclosure at page 6, lines 10-13. As discussed therein, a protective group may be comprised either at the amino-terminal end or carboxy-terminal end of the peptide, or at both ends, for example by acetylation of the amino terminal end or amidation of the carboxy terminal end of the peptide.

With respect to the Examiner;s query concerning the concentration of the tripeptide, Applicants respectfully note that this refers to the amount of the tripeptide, i.e., the active moiety. The objection to Claims 12-14 is rendered moot by the cancellation of these claims herein. Similarly, the objection to Claim 15 is moot based on the cancellation of this claim. Based on the foregoing, withdrawal of the §112, second paragraph, rejection of Claims 1-15 is respectfully requested.

Claims 1-3 and 12 stand rejected under 35 U.S.C. §102(b) as being anticipated by Ferreira et al (U.S. Patent 5,389,615) or Oluyomi et al (*European Journal of Pharmacology*, 258:131

(1994)). These rejections are respectfully traversed to the extent they may be applicable to the claims as amended.

As properly summarized by the Examiner, the Ferreira reference teaches the use of a tripeptide K(d)PV for the treatment of pain. However, contrary to the Office Action, treatment of pain can not be equated to inflammation. Therefore, this reference would not teach or suggest the use of the subject tripeptide for the treatment of inflammation as claimed herein. They cannot be equated as pain results from numerous causes other than inflammation, e.g., trauma, burn, etc.

Similarly, Oluyomi et al fails to teach or suggest the use of the subject tripeptides for the treatment of inflammation. Rather, this references suggests the anti-nociceptive activity of peptides including lys-pro-thr. This reference, however, fails to teach or suggest the use of such peptides for the treatment of inflammation. Rather, this reference instead relates to the use of this peptide for inhibition of painful sensations. In this regard, nociceptive is defined as receiving?? painful sensations elicited by receptive neurons. For the Examiner's convenience, a page from Dorland's Illustrated Medical Dictionary, containing a definition of "nociceptive" is attached to this Reply. Therefore, it is clear that neither Ferreira or Oluyomi et al anticipates or suggests the claimed invention, as pain can not be equated to inflammation.

Claims 4, 7-10 and 15 further stand rejected under 35 U.S.C. §103 as being unpatentable over Ferreira et al. This rejection is also respectfully traversed on the basis that this reference does not teach or suggest the use of this tripeptide for the inhibition of inflammation. To the contrary, the reference is directed to the usage of this peptide for the treatment of pain. This is apparent for example from the abstract and the disclosure in its entirety. Moreover, it is further apparent from the examples, all of which describe the effects of the exemplified peptides on hyperalgesia, i.e., excessive sensitivity or sensibility to pain. A definition for "hyperalgesia" is also attached for the Examiner's convenience. Therefore, withdrawal of the §103 rejection of Claims 4, 7-10 and 15 based on Ferreira is respectfully requested.

Claims 5-6 further stand rejected under 35 U.S.C. §103 as being unpatentable over Ferreira et al and further in view of Lipton (U.S. Patent 5,157,023) and Oluyomi et al (*European Journal of Pharmacology*, 258:131 (1994)).

As discussed, *supra*, both Ferreira and Oluyomi et al fail to teach or suggest the claimed invention. To the contrary, these references relate to the use of peptides including lys-pro-val for the treatment of pain. However, they do not teach or suggest the use of such tripeptide for treatment of inflammation as claimed herein. Moreover, the deficiencies of these references are not cured by Lipton. Lipton is relied upon to

suggest the use of protected peptides in favor of non-protected peptides (in order to achieve enhance stability). Essentially, the reference explains that such protected peptides may exhibit enhanced resistance to enzymatic attack and degradation. This is acknowledged to have been known prior to the present invention. However, this reference likewise would not teach or suggest the present invention, as it does not suggest use of the specific protected peptide forms recited in the claimed methods for the treatment of inflammation. Therefore, based on the foregoing, withdrawal of the §103 rejection based on Ferreira taken in view of Lipton and Oluyomi et al is respectfully requested.

Claims 1-15 further stand rejected based on Ferreira et al in view of Nordlund (U.S. Patent 4,874,744), Lipton, and Remington's Pharmaceutical Sciences, CH87 and 92, and Oluyomi et al.

As discussed above, Ferreira et al and Oluyomi fail to teach or suggest the claimed invention as these references fail to teach or suggest the use of the lys-pro(d)-val containing peptides for the treatment of inflammation. To the contrary, these references are limited to the use of such peptides for the treatment of pain. As discussed above, it is improper for the Examiner to equate pain and inflammation, as these phenomena may arise from different causes. While inflammation <u>may</u> result in pain, it is not proper to equate pain with inflammation, as pain can also result from traumatic injury, as well as numerous other causes. Also, inflammatory responses do not elicit pain.

Moreover, the deficiencies of these references are not cured by Nordlund, Lipton or Remington's Pharmaceutical Sciences. Lipton is applied as above, namely to suggest the usage of protected peptides in favor of non-protected peptides. However, this reference likewise fails to teach or suggest the use of a specific tripeptides for treating inflammation.

Moreover, Nordlund is cited based on its disclosure relating to topical application of peptides for treatment of inflammation. Specifically, it teaches topical application of alpha MHS for treatment of inflammation. However, as with the other references, this reference fails to teach or suggest the use of the specific tripeptides for treatment of inflammation. Therefore, it also fails to teach or suggest the claimed invention.

Finally, Remington's is relied upon based on its disclosure relating to topical treatments and aerosols for treatment of inflammation. However, this reference also fails to teach or suggest the use of the specific tripeptide comprising lysine-proline-valine for the treatment of inflammation.

Therefore, based on the foregoing, withdrawal of the §103 rejection based on Ferreira, taken in view of Nordlund, Lipton, and Remington's Pharmaceutical Sciences and Oluyomi, is respectfully requested as these references separately or in combination fail to teach or suggest the use of lysine-proline-valine containing peptides for the treatment of inflammation.

Claims 1-3 and 5-15 further stand rejected under 35 U.S.C. §103 as being unpatentable over Oluyomi et al in view of Nordlund, Lipton, and Remington's Pharmaceutical Sciences. This rejection is also respectfully traversed.

As discussed above, Oluyomi et al fails to teach or suggest the present invention as it is limited to the use of such peptides for the treatment of pain. However, as discussed above, pain can not be equated to inflammation. In this regard, it is well known that pain can result from a myriad of causes, including, but not limited to, inflammation. Therefore, one skilled in the art could not reasonably suggest that a compound suitable for use for inhibiting pain would necessarily have any effect on inflammation.

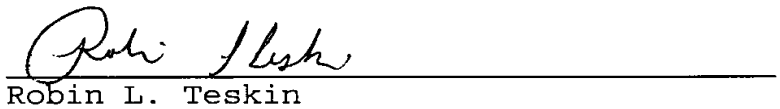
The secondary references do not cure the deficiency of Oluyomi et al, since they likewise fail to teach or suggest the use of the subject tripeptide for treatment of inflammation. Rather, they are merely relied upon for their disclosure relating to the use of protected peptides in lieu of non-protected peptides, and topical application of peptides for treatment of inflammation. This is acknowledged to have been known prior to the present invention, however, such disclosure fails to render obvious the claimed invention. Essentially, the secondary references suffer from the same deficiencies as the primary reference. Specifically, they fail to teach or suggest the use of lys-pro-val (D) peptides for the treatment of inflammation.

Therefore, based on the foregoing, withdrawal of the §103 rejection based on Oluyomi taken in view of Nordlund, Lipton and Remington's Pharmaceutical Sciences is respectfully requested.

Based on the foregoing, this application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited. However, if any issues remain outstanding after consideration of this reply, the Examiner is respectfully requested to contact the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: 

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